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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GARVEY, TARA L	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 08/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/832,621	RAUCY, JUDY	
	Examiner	Art Unit	
	Tara L Garvey	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *150-205* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *150-159, 161-189 and 191-205* is/are rejected.

7)☒ Claim(s) *160 and 190* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 27, 2003 has been entered.

Claims 84-149 were considered in the Final Office action mailed February 11, 2004. Claims 1-149 were canceled in the remarks filed on June 21, 2004. Claims 150-205 are pending in this application.

Priority

This application is given priority to provisional application 60/241,391 filed on 10/17/2000.

Response to Arguments

While Applicant's arguments generally no longer apply due to the cancellation of claims 1-149, to the extent that they still apply are addressed below. Applicant does not believe that Windmill et al renders it obvious to use other cell types. Windmill et al demonstrated that the CYP genes are expressed in multiple tissues and the use of additional cell types would have been obvious.

New grounds of rejection, necessitated by Applicants' amendment, are presented below.

Claim Objections

Claim 175 is objected to because of the following informalities: Please remove the "c" after "The". Appropriate correction is required.

Claim 178 is objected to because of the following informalities: The word "trasfected" should be spelled "transfected". Appropriate correction is required.

Claim 181 is objected to because of the following informalities: The word "enahncer" should be spelled "enhancer". Appropriate correction is required.

Claims 160 and 190 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 161-163 recites the limitation "said nucleic acid molecule encoding CYP3A4" in line 3. The nucleic acid in claim 176 from which each of these claims depends contains a "promoter or enhancer operable for a nucleic acid molecule encoding CYP3A4, and a reporter gene." There is insufficient antecedent basis for this limitation in the claim.

Claims 191-193 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The use of the phrase "produces transcriptional activation of a gene encoding CYP3A4" is unclear because in the assay the CYP3A4 gene is not actually encoded by the expression plasmid, instead a regulatory region of the CYP3A4 gene controls the expression of a reporter gene.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 150-158, 161-164, 167-172, 176-177, 181-188, 191-194 and 197-202 are rejected under 35 U.S.C. 102(a) as being anticipated by Liddle et al (WO 99/61622).

Claim 150 is drawn to a recombinant cell that comprises one nucleic acid that containing a reporter gene and a promoter or enhancer element of CYP3A4, which controls the expression of the reporter gene and a second nucleic acid that encodes PXR. Either nucleic acid can be stably transfected into the cell. When the cell is treated with a compound, the reporter gene is expressed due to the interaction of PXR with the CYP3A4 regulatory element. Claims 151-153 further limit the invention of claim 150 to a promoter or enhancer that comprises PXRE, XREM, or both PXRE and XREM. Claims 154-155 limit the invention of claim 150 to a reporter gene that is an enzyme or

a detectable protein. Claims 156-157 limits the invention of claim 150 to the first nucleic acid being extrachromosomal or within the chromosome of the cell. Claim 158 limits the invention of claim 150 to the reporter gene being inserted into the chromosome of the cell. Claims 161-163 limit the invention of claim 150 to PXR forming a complex or being indirectly activated by a compound, which results in the transcriptional activation of the CYP3A4 regulatory element-reporter gene construct. Claim 164 limits the invention of claim 150 to the second nucleic acid which encodes PXR being in the extrachromosomal area of the cell. Claims 167-172 limits the invention of claim 150 to the type of cell.

Claim 176 is drawn to a method for evaluating compounds that induce the expression of CYP3A4 by contacting a test compound with a recombinant cell that comprises a first nucleic acid molecule containing a reporter gene and a promoter or enhancer element of CYP3A4, which controls the expression of the reporter gene and a second nucleic acid that encodes PXR. When the cell is treated with a compound, PXR forms a complex with or is indirectly activated by a compound and the reporter gene is expressed due to the interaction of PXR with the CYP3A4 regulatory element. The detection of the reporter gene is indicative of the altered expression of a gene encoding CYP3A4. Claim 177 limits the invention of claim 176 to the first nucleic acid being stably transfected into the cell. Claims 181-183 limit the invention of claim 176 to a promoter or enhancer that comprises PXRE, XREM, or both PXRE and XREM. Claims 184-185 limit the invention of claim 176 to a reporter gene that is an enzyme or a detectable protein. Claims 186-187 limit the invention of claim 176 to the first nucleic

acid molecule being an extrachromosomal element or being within the chromosome of the cell. Claim 188 limits the invention of claim 176 to the reporter gene being inserted into the chromosome of the cell. Claims 191-193 limit the invention of claim 176 to PXR forming a complex or being indirectly activated by a compound, which results in the transcriptional activation of the CYP3A4 regulatory element-reporter gene construct. Claim 194 limits the invention of claim 176 to the second nucleic acid which encodes PXR being in an extrachromosomal area of the cell. Claims 197-202 limits the invention of claim 176 to the type of cell.

Liddle et al teach a construct containing CYP3A4 regulatory elements such as PXRE and XREM and a reporter gene that can encode a detectable protein such as luciferase or green fluorescent protein (page 3 lines 21-31, page 4 lines 2-3, page 14 lines 30-35 and page 16 lines 3-10) and transfection of this construct either as an extrachromosomal element or by incorporation into the chromosome of any cell type (page 4 lines 21-23 and page 25 claim 25). In addition, they teach cotransfection of HepG2 cells with hPXR expression vector and the CYP3A4-XREM-reporter construct in the presence of various drugs to determine the effect of the compounds on CYP3A4 gene transcription (page 6 lines 12-20 and page 16 lines 1-16). Thus, Liddle et al teach all that is recited in the instant claims.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 176, 181, 184, 186, 191-194, 197-199, 201 and 205 are rejected under 35 U.S.C. 102(b) as being anticipated by Lehmann et al (Journal of Clinical Investigation, (1998), volume 102, issue 5, pages 1016-1023).

Claims 176, 181, 184, 186, 191-194, 197-199, 201 and 205 have been described previously.

Lehmann et al teach transfection of CV-1 kidney cells with a PXR expression plasmid and a reporter plasmid containing a CYP3A4 PXRE regulatory element and a reporter gene such as CAT, treatment of the transfected cell with various compounds and detection of reporter gene expression as an indication of the effect of the interaction of the compound and PXR on the regulation of CYP3A4 gene expression (page 1017, left column, second full paragraph, lines 15-18; page 1019, right column, second paragraph, lines 11-18 bridging page 1020, lines 1-3; page 1020, lines 1-15). Thus, Lehmann et al teaches all that is recited in the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 150, 165, 176, 178, 179 and 195 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liddle et al (WO 99/61622).

Claims 150 and 176 have been described previously. Claim 165 limits the invention of claim 150 to the second nucleic acid encoding PXR being within the chromosome of the cell. Claim 178 limits the invention of claim 176 to the second nucleic acid being stably transfected into the cell. Claim 179 limits the invention of claim 176 to both the first and second nucleic acids being stably transfected into the cell. Claim 195 limits the invention of claim 176 to the second nucleic acid being within the chromosome of the cell.

Liddle et al teaches the incorporation of the first nucleic acid containing a CYP3A4 regulatory element and a reporter gene, but does not explicitly teach the insertion into the chromosome of the second nucleic acid expressing PXR. It would have been obvious to one of ordinary skill in the art to modify the teachings of Liddle et al to stably transfect the PXR expression vector into the cell because Liddle et al teach that it is within the skill of the art to incorporate nucleic acids into the host chromosome of the host cell. One would have been motivated to do so in order to receive the expected benefit of, as suggested by Liddle et al maintaining the expression of a gene in a cell at a desired level and avoiding the need transfect the cells for each experiment. Absent of any evidence to the contrary, there would have been a reasonable expectation of success in stably transfecting PXR into the cell since it is known that single and double gene stable cell lines can be made and successfully express the desired genes at detectable levels.

Claims 150, 173-176 and 203-205 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liddle et al (WO 99/61622) in view of Windmill et al (Mutation Research, (1997), volume 376, pages 153-160).

Claims 150 and 176 have been described previously. Claims 173-175 limit the invention of claim 150 to gastrointestinal tract, lung or kidney cells. Claims 203-205 limit the invention of claim 176 to gastrointestinal tract, lung or kidney cells.

Liddle et al teach the recombinant cell of claim 150 and used in the method of claim 176 as a liver cell, but not a gastrointestinal, lung or kidney cell. Windmill et al demonstrates that at the time of the invention it was known that a cytochrome P450 enzyme was expressed in "human liver, stomach, small and large intestine, gall bladder, appendix, lung, kidney and adrenals" (page 156, left column, lines 11-19). They further demonstrate that CYP3A4 is the main P450 enzyme in the human small intestines and the liver (Page 156, right column, lines 4-7). It would have been obvious to one of ordinary skill in the art to modify the teachings of Liddle et al to also use cells from the gastrointestinal tract, the lung and the kidney because Liddle et al teach that it is within the skill of the art to use any cell type to test compounds that will bind or activate PXR and cause the expression of the reporter gene controlled by a CYP3A4 regulatory element. One would have been motivated to do so in order to receive the expected benefit of, as suggested by Liddle et al and actually exemplified by Windmill et al, of using cells from the gastrointestinal tract, the lung and the kidney to test compounds that are involved in the regulation of the CYP3A4 gene expression. Absent of any evidence to the contrary, there would have been a reasonable expectation of success in

using gastrointestinal tract, lung or kidney cells since it has been shown that CYP genes are expressed in these tissues.

Claims 176, 180, 182, 184, 186, 194, 197-199, 201 and 205 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liddle et al in view of Collins et al (US Patent 6,579,686). Claims 176, 182, 184, 186, 194, 197-199, 201 and 205 have been described previously. Claim 180 limits the invention of claim 176 to a high throughput method. Liddle et al teach the method of claim 176, but do not teach a high throughput method. Collins et al demonstrate the transient transfection of CV-1 kidney cells in a 96-well plate format with a CAR (a receptor related to PXR) expression vector and CYP3A4-XREM-luciferase reporter construct, treatment of the cells with a compound, and measurement of luciferase activity, which is indicative of the compounds ability to alter the expression of CYP3A4 gene expression (column 3 lines 29-36, column 6 lines 46-67 bridging column 7 lines 1-2 and column 8 lines 35-52). The use of this high throughput method was well known at the time if this invention. It would have been obvious to one of ordinary skill in the art to modify the teachings of Liddle et al to perform the transfections in a 96-well plate high throughput format. One would have been motivated to do so in order to receive the expected benefit of, as suggested by Liddle et al and actually exemplified by Collins et al of being able to screen more compounds and conditions in one experiment. Absent of any evidence to the contrary, there would have been a reasonable expectation of success in using the 96-well plate format since it is known that the transfection of cells and the analysis of an assay can be performed in a 96-well plate.

Claims 150, 159, 165, 166, 176, 189, 195 and 196 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liddle et al (WO 99/61622) in view of Lehmann et al (Journal of Clinical Investigation, (1998), volume 102, issue 5, pages 1016-1023) and Pascussi et al (Molecular Pharmacology, (2000), volume 58, pages 361-372).

Liddle et al teaches the transfection of cells with the CYP3A4 reporter construct and the PXR expression vector, but does not teach transfection of cells that contain the CYP3A4 regulatory element in their chromosome or endogenously express PXR. Lehmann et al demonstrate that liver cells and small intestine cells express CYP3A4 and PXR (page 1018, first full paragraph, lines 3-5). Pascussi et al demonstrates that human liver cells treated with a compound such as dexamethasone induces PXR expression and induces CYP3A4 expression in response to known PXR activators (abstract, page 362, right column, first full paragraph, lines 1-4, page 366, right column, first full paragraph, last 4 lines). It would have been obvious to one of ordinary skill in the art to modify the teachings of Liddle et al to perform the transfections in human hepatocytes because these cells have been shown to endogenously express CYP3A4 and PXR. One would have been motivated to do so in order to receive the expected benefit of, as suggested by Liddle et al and actually exemplified by Lehmann et al and Pascussi et al to use a cell that endogenously expresses CYP3A4 or PXR in order to see the level of expression in a natural occurring situation and to avoid the need for cotransfection of both molecules. Absent of any evidence to the contrary, there would have been a reasonable expectation of success in using a human hepatocyte since it

has been shown that compounds induce the expression of PXR which then up-regulates the expression CYP3A4 in this cell type.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tara L Garvey whose telephone number is (571) 272-2917. The examiner can normally be reached on Monday through Friday 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) (http://pair-direct.uspto.gov) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the

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Tara L Garvey
Examiner
Art Unit 1636

TLG

JAMES KETTER
PRIMARY EXAMINER